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10/047,945	01/14/2002	Binic V. Lipps	FWLPAT015US	5192

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EXAMINER
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SZPERKA, MICHAEL EDWARD

ART UNIT	PAPER NUMBER
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1644

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**MAILED**  
**APR 10, 2006**  
**GROUP 1600**

**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

Application Number: 10/047,945  
Filing Date: January 14, 2002  
Appellant(s): LIPPS ET AL.

John R. Casperson  
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed 3 February 2006 appealing from the Office action mailed 28 June 2005.

**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

**(2) Related Appeals and Interferences**

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**(3) Status of Claims**

The statement of the status of claims contained in the brief is correct.

**(4) Status of Amendments After Final**

No amendment after final has been filed.

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter contained in the brief is correct.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

**(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(8) Evidence Relied Upon**

US-5,576,297	LIPPS et al.	11-1996
US-5,744,449	LIPPS et al.	4-1998

Catanese et al., "Isolation from Opossum Serum of a Metalloproteinase Inhibitor Homologous to Human alpha1B-Glycoprotein" *Biochemistry*, 31:410-418 (1992)

Perales et al. "Isolation and Partial Characterization of an Anti-Bothropic Complex from the Serum of South American Didelphidae" *Toxicon*, vol 32, no. 10, pages 1237-1249, (1994)

Beer and Berkow, editors, The Merck Manual of Diagnosis and Therapy, 17th edition, Merck & Co. Inc, pages 165-177 and 1531-1538 (1999)

**(9) Grounds of Rejection**

The following ground of rejection is applicable to the appealed claims:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Appellant has claimed a method for reducing free serum immunoglobulin E (IgE) by administering a peptide that comprises at least the first four amino acids of SEQ ID NO:2 in all examined claims excepting dependent claim 13 wherein the administered peptide is selected from the group consisting of SEQ ID NOs; 1, 4, 5, 6, and 7. SEQ ID NO:2 of the instant application is a 15 amino acid peptide that has the sequence LKAMDPTPPLWIKTE, and SEQ ID NOs; 1, 4, 5, 6, and 7 are all fragments that are completely contained within SEQ ID NO:2. Catanese et al. isolated a snake venom metalloproteinase inhibitor from opossum that shared homology with human  $\alpha$ 1B-glycoprotein, and that contained more than the first four amino acids of SEQ ID NO:2 (Biochemistry 1992, 31:410-418, see entire document particularly the abstract and Table V on page 417). Perales et al. demonstrated that this metalloproteinase inhibitor could also be isolated from South American opossums, and report a sequence for the amino terminal portion of the protein that comprises SEQ ID NO:2 (Toxicon, 1994, 32:1237-1249, see entire document particularly the abstract and page 1245). Lipps et al. further disclosed in US Patent numbers 5,576,297 and 5,744,449 that a peptide

identical to SEQ ID NO:2, as well as peptides comprising at least 3 amino acids of this sequence, have the biological property of inhibiting the lethal effects of venom from poisonous snakes (see entire documents, particularly claim 9 of the '449 patent). As such, the prior art clearly demonstrates that the peptide of SEQ ID NO:2 as well as fragments of SEQ ID NO:2 were known to be inhibitors of metalloproteinases found in snake venom.

Appellant has asserted that the metalloproteinase inhibiting peptide of SEQ ID NO:2 and its derivatives (i.e. SEQ ID NO: 1, 4, 5, 6, and 7, and peptides comprising at least the first four amino acids of SEQ ID NO:2) can be used to reduce the levels of various serum proteins and treat numerous diseases, and that all of the above peptides have similar biological activity (see particularly lines 8-20 of page 7 and lines 23-25 of page 5 of the instant specification). Specifically, appellant asserts that the specification contains data to support the conclusion that administration of the peptide of SEQ ID:1 causes a decrease in IgE levels, and that numerous disorders including diabetes, depression and autoimmunity are caused by high levels of IgE (see particularly Table 1, Table 2, the paragraph that spans pages 12 and 13 of the specification, and note that SEQ ID NO:1 is a 10 amino acid polypeptide of sequence LKAMDPTPPL). High levels of IgE are not recognized in the art as being correlated with the recited diseases such as diabetes and depression, and as such high levels of IgE are certainly not recognized as causing said diseases (The Merck Manual, seventeenth edition, 1999, see particularly pages 165-177 and pages 1531-1538). The data presented in Tables 1 and 2 is not convincing to a person of skill in the art that a correlation, let alone a causal

relationship, exists between IgE levels and the indicated diseases because no statistical measurements were performed to demonstrate that the observed results were not due to random chance. The influence of random chance is quite high given that only one individual was measured in both diabetes and depression (note that the pooled diabetic sample is not meaningful since it contains material from just two individuals and a high value from one of the samples would mask a low value in the other sample). No indication is given that experiments such as those in Tables 1 and 2 were ever repeated or that they are reproducible.

On page 8, lines 11-23 of the specification, appellant provides experiments intended to demonstrate the IgE reducing properties of the peptide of SEQ ID NO:1. No data concerning these experiments are provided, so it is not clear how appellant has determined that the peptide of SEQ ID NO:1 binds to IgE, although it appears that appellant's failure to detect IgE in samples treated with the peptide of SEQ ID NO:1 has lead to this conclusion (see particularly page 8, lines 14-17 and 21-23). Briefly, Experiment 1 is a closed system wherein saliva is mixed with either PBS or the peptide of SEQ ID NO:1 (what it is dissolved in is not specified) in a closed tube, incubated at 37°C for one hour, and then assayed for the presence of IgE. Experiment 2 involves appellant placing a volume 1 ml of either water or a solution containing 1mg/ml SEQ ID NO:1 in appellant's mouth for 15 minutes, and then measuring the IgE content of oral cavity liquids. Both measurements are disclosed as being done by ELISA.

As stated earlier, SEQ ID NO:1 is a metalloproteinase inhibitor that is 10 amino acids in length. It is not an enzyme, so it would not be expected to have degraded the



IgE present in the solution. It is not clear why the binding of SEQ ID NO:1 to IgE, if it even binds, would make IgE undetectable in appellant's experiments, especially the closed system of Experiment 1. Since the epitope recognized by the anti-IgE antibody used by appellant is not specified, the only logical way that peptide binding to IgE could render the IgE undetectable is if the peptide masks the epitope on IgE recognized by the anti-IgE antibody. If this is so, peptide binding does not reduce IgE levels since IgE would still be detectable if an anti-IgE polyclonal sera or an anti-IgE antibody that recognizes a different epitope is used in the detection assay. Further, there is no indication that the experiments conducted by appellant were ever repeated. As such, the findings of appellant's Experiments 1 and 2 can also be quite reasonably explained as being due to random chance and not due to any effect of the peptide of SEQ ID NO:1 on binding IgE and reducing free IgE levels.

Additional data concerning the administration of the peptide consisting of SEQ ID NO:1 can be found in Tables 3-7. The measurements of IgE presented in these tables were presumably obtained using the same diagnostic assay described above for experiments 1 and 2, and as such it appears reasonable the reported data would not show any difference in IgE levels if an anti-IgE antibody of differing or multiple epitope specificity was used to collect the data. The data presented in Tables 3-7 was obtained by repeated measurements of just one individual, inventor Binie Lipps. No statistical measurements were performed to demonstrate that the observed differences were significant, or that such differences could be obtained by treating a different individual.

As such, one of skill in the art could also quite reasonably conclude that the observed differences were not due to anything more than random chance.

The statistical significance of any of the above-described experimental data has not been provided. As such, there is no reason that a skilled artisan would believe that the indicated effects of administration of a peptide consisting of SEQ ID NO:1 are due to anything more than random chance, especially since there is no indication that any of the experiments were repeated. Given the doubtful nature of the guidance and working examples in the specification including their lack of statistical validity, the fact that the prior art does not recognize that the claimed genus of peptides, or of metalloproteinase inhibitors in general, have the claimed biological property of reducing IgE levels, the fact that the prior art also does not recognize a correlation between IgE levels and the instant recited diseases, and the general unpredictable nature of biological systems, an undue amount of additional research would be required to practice appellant's claimed method.

#### **(10) Response to Argument**

Appellant's arguments filed 3 February 2006 have been fully considered but are not found persuasive.

Appellant argues that the examiner has improperly set forth an enablement rejection because appellant believes that the examiner has ignored one or more of the factors indicated in *In re Wands*. The examiner's position is that all Wands factors

relevant to the instant claimed invention were adequately addressed in the office actions of record.

### The Breadth of the Claims

Appellant argues that limitations of claims 17 and 18 as currently amended have not been adequately addressed, and that much of the rejection of record concerning binding, correlation of IgE levels with disease, and antibodies have no bearing on claim 9. The examiner disagrees.

Claims 17 and 18 as currently amended indicate that the human to whom appellant's disclosed peptides are administered have specific conditions or diseases, and as such they indicate an intended patient population for appellant's claimed method. The examiner cited the Merck Manual of Diagnosis and Therapy during prosecution to indicate that there is no art recognized correlation between the recited diseases and serum IgE levels. This is important because the specification teaches in the sentence that spans pages 12 and 13 of the specification that "Collectively, the results of Tables 1 and 2 clearly show that the elevated level of IgE is the culprit-causing numerous types of disorders" and Tables 1 and 2 list patients suffering from diabetes, asthma, depression, and autoimmune disease. Appellant argued on page 8 of the response received April 10, 2005, that claims 17 and 18 as amended required reducing free IgE in humans having the recited conditions but that the claim language did not require any causation or effectiveness against the disease. Claims are to be read in light of the specification, and as indicated above, the specification is quite

explicit in indicating that increased IgE levels cause the recited diseases. Further, claim 5 (currently withdrawn) recites "Decrease in IgE level brings the homeostasis of other proteins to normal state which improves the symptoms in the afflicted people for asthma, depression, diabetes and various types of autoimmune diseases, such as erythematosus (SLE); Rheumatoid arthritis Sjogren's syndrome; Reiter's syndrome; Diabetes mellitus (insulin dependent); Graves' disease; Addison's disease Hodgkin's disease etc." Such changes in claim language, and appellant's statement in the reply received April 10, 2005 that causation or therapeutic efficacy are not recited, were specifically addressed in the final action mailed June 28, 2005, wherein the issue was raised as why a skilled artisan would use appellant's claimed method to reduce free IgE levels in the recited patient populations if reducing free IgE levels in these patients has no therapeutic value. Appellant does not appear to have responded this issue in the appeal brief, other than indicating that the instant claims have not been rejected under 35 U.S.C. 101. The specification clearly states that reducing IgE is therapeutically beneficial for a wide variety of diseases and if appellant no longer believes this to be true (hence the wording of the instant claims and the specific argument that causation or therapeutic efficacy are not claimed in the response received April 10, 2005) it is unclear what other rationale is disclosed in the specification for why a skilled artisan would reduce IgE levels.

Appellant has also indicated that a discussion concerning peptide binding and antibodies is not relevant to claim 9 on appeal. The examiner disagrees, since a discussion of how administering appellant's peptides mechanistically works to achieve

the recited reduction in free IgE levels, or indeed if administration does in fact reduce IgE levels, is critical to the claimed invention and such a discussion of appellant's method as recited in claim 9 necessarily involves peptide binding and antibodies. See the grounds of rejection.

#### The Nature of the Invention

Appellant argues that the examiner has not characterized the invention in reference to the claims. The examiner disagrees. See the entirety of the office actions mailed 24 January 2005 and 28 June 2005, most particularly pages 5 and 6 of the office action mailed 24 January 2005. The examiner agrees that the claimed concept, as summarized by appellant as "administer X to accomplish Y" is correct. However, the basis for the enablement rejection is that the examiner is not convinced that the specification clearly demonstrates to a skilled artisan that administering X (i.e. SEQ ID NO:2 and its derivatives) accomplishes Y (reducing free IgE levels) and has provided scientific reasoning to support this position. See the grounds of rejection.

#### The State of the Prior Art

Appellant argues that the examiner's position is that appellant's assertion of reducing free IgE with peptides is not credible because it has not been done in the prior art. Appellant is correct that reducing IgE with appellant's peptides is not taught in the art, but appellant is incorrect in stating that this is the examiner's only rationale for doubting appellant's assertions and data. The examiner has set forth on the record and

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argument based upon scientific reasoning concerning how the data provided by appellant does not support the conclusions appellant has made concerning said data.

See the grounds of rejection.

The Level of One of Ordinary Skill

The examiner agrees that the level of skill in the art is quite high, and this is not an issue pertinent to the instant claimed methods.

The Level of Predictability in the Art

Appellant is correct that the specification states that the peptides of SEQ ID NO:2, 1, and 3 (LT-15, LT-10 and LT-5 respectively) have equivalent biological activity. The prior office actions questioned appellant's characterization of this biological activity based upon interpretation of the data presented concerning SEQ ID NO:1 and as such the discussion of this data concerning the use of SEQ ID NO:1 present in the prior office actions is equally applicable to all of appellant's peptides since they are all taught as having equivalent biological activity. See the grounds of rejection.

The amount of direction provided by the inventor

Appellant argues that the examiner ignored the fact that the specification identifies peptides, teaches administration of said peptides, and teaches how to measure IgE levels. The examiner did not ignore these issues since as was indicated in the prior office actions, the peptides are taught in prior art patent and non-patent

documents. Further, skilled artisans are well aware of how to administer a peptide and methods for measuring IgE. Given that appellant does not teach novel routes of delivery or other techniques that would not be known to skilled artisans for administering peptides, this issue is not pertinent to the claims on appeal. Further, appellant's claimed invention is not a method of detecting IgE, and as such a discussion of this issue is only relevant as it applies to how appellant collected the data provided in the specification, how this data is most correctly interpreted, and if such interpretations support appellant's conclusions concerning the administration of peptides, IgE levels, and the presence of disease states. Such issues have been discussed in the grounds of rejection.

The existence of working examples

Appellant argues that the data and teachings of the specification were dismissed by the examiner for lack of statistical validation. The examiner did not dismiss the teachings and data outright based upon lack of statistical validation, but when coupled with the fact that the prior art does not teach or fairly suggest that a peptide known to inhibit metalloproteinases also reduces IgE levels and the difficulty in determining how administration of said peptide caused the recited effect of reducing free IgE levels, the lack of statistical relevance of the data indicates that the conclusions drawn by appellant are likely due to random chance. See the grounds of rejection.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure

Appellant argues that the specification is fully enabling and that no additional data is required. Appellant indicates that the provided data was obtained from a human, and that the office cannot require additional human clinical trials.

Appellant is correct that inventor Binie Lipps experimented on herself to provide data disclosed in the specification, and this was noted by the examiner on page 7 of the office action mailed January 24, 2005. Appellant is also correct that appellant is not required to conduct human clinical trials. However, given the issues concerning how to interpret the results of Experiments 1 and 2 found on page 8 of the specification as well as the data presented in Tables 1-7, the lack of a discussion in the specification or art as to the mechanism by which administering a peptide that inhibits metalloproteinases reduces free IgE levels, and the lack of statistical significance in the data presented by appellants, a skilled artisan would not be reasonably convinced that claimed method would result in the recited outcome, namely a reduction in free IgE levels. As such, a skilled artisan would need to conduct an undue amount of additional research before being able to practice appellants claimed method. See the grounds of rejection.

**(11) Related Proceeding(s) Appendix**



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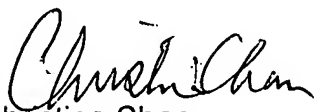
No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

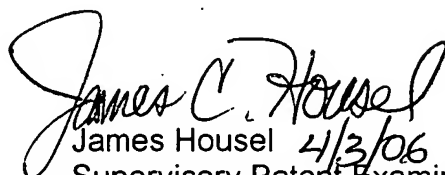
For the above reasons, it is believed that the rejections should be sustained.


Respectfully submitted,

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